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Concept of Polycystic Ovarian Syndrome: Causes, Prevention and Management

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Abstract
Introduction: *Polycystic ovarian syndrome (PCOS) is one of the common reproductive and endocrine disorder in women of reproductive age group. Around one out of every five Indian women suffer from PCOS.*
Risk factors & Causes: *The cause of PCOS depends on individual to individual but the exert cause of PCOS is unknown whereas, some associated risk factors are environmental chemical, food adulteration, excess insulin, obesity, lack of exercise and unhealthy lifestyle practices.*
Sign & Symptoms: *The symptoms of PCOS vary from patient to patient however, some associated symptoms of PCOS includes menstrual irregularities, acne, pelvic pain, acanthosis nigricans, hirsutism and weight gain which significantly impacts their quality of life. Currently, PCOS must be consider a serious issue in reproductive age women and it also a silent killer because it cannot be diagnosed by single diagnostic evaluation method.*
Prevention & Management: *Polycystic ovary syndrome is a complex disorder which required multiple strategies for treatment of PCOS. The treatment is vary because it depend on the causes of PCOS. Therefore, various common strategies used for management of PCOS such as adopting healthy lifestyle practices, medical management and also rarely require surgical management. However, complementary therapy also being helpful to prevent and in the management of PCOS which includes yoga, acupuncture and homeotherapy.*
Conclusion*: PCOS is the common hormonal disorder in reproductive age group women. The causes, sign and symptoms of PCOS vary from individual to individual. The common prevention strategies used for management of PCOS such as adopting healthy lifestyle practices, medical management and also rarely require surgical management.*

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I. Introduction:

Childbirth is a unique experience for every women and wants to get pregnant in her life but due to various reproductive problems they are unable to conceive. There are various reason to causes for infertility in female in which one of the most common cause of infertility is polycystic ovarian syndrome. It is a complex endocrine disorder associated with anovulation, insulin resistance, hirsutism and an excess of androgens circulating in the blood of women.

Formation of cystic in ovaries is a morphological feature of PCOS and biochemical feature comprise hyperandrogenemia. The polycystic ovarian syndrome has been associated with an increased risk for cardiovascular diseases, Type 2 diabetes, gestational diabetes, hypertension, and gynecological cancers.[1]

Polycystic ovarian syndrome characterized by formation of cysts in the ovaries, include hirsutism, obesity, menstrual irregularities, infertility and acne. Hyperandrogenism is a clinical hallmark of PCOS, be able to cause inhibition of follicular development, micro cysts in the ovaries, anovulation, menstrual changes and infertility.[2]

II. Ovary and its Functions:

Polycystic ovary syndrome (PCOS) is an umbrella term used to make a group of symptoms that appear to be connected with menstrual cycle and to have a strong correlation with insulin sensitivity. Ovaries are important female reproductive organ which is situated on either side of the uterus beside the pelvic wall.

The Ovarian glands play important functions in reproductive age women which protect the ova until ready for fertilization, it is also secrete hormones such as estrogen, progesterone, relaxin, inhibin and ovulation. Women suffering from PCOS encompass a hormonal imbalance and metabolism disturbance that affect overall health and appearance of women. In present, PCOS is also a common and manageable cause of infertility.

Normal Ovarian Cycle:

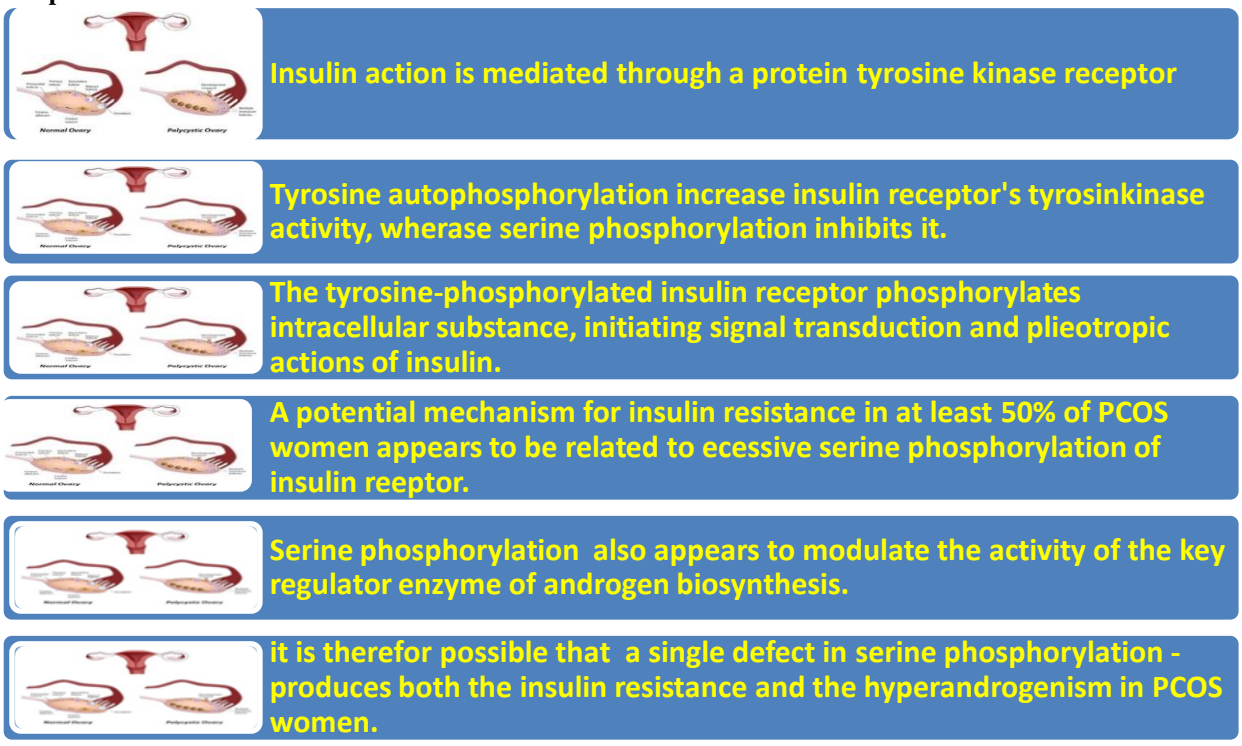
Normally in each hormonal cycle pituitary gland releases a hormone which helps the ovaries to produce a multiple follicles. 7th day of menstrual cycle, only one follicle continues mature and other follicles inhibit to growing, on the days 12th of menstrual cycle the amount of oestrogen increase into the blood stream. The oestrogen hormone circulate through blood as it is reaches to pituitary gland, the pituitary gland responds by releasing the luteinizing hormone which helps to rapture of mature follicle. Following rupture of mature follicle fimbriae pick up the egg and transported to the fallopian tube. If fertilization occurs then the fertilized egg move into the fallopian tube and move forward towards the uterus for implantation. Meanwhile, fertilization not occur then shedding of endometrium will start and next menstrual cycle begin.

Pathogenesis of PCOS:

Pathophysiology of polycystic ovary syndrome remains unknown, but there is growing accord it may discussed under key features which include insulin resistance, androgen excess and abnormal Gonadotropin dynamics.[10] Several theories have been proposed to explain the pathogenesis of polycystic ovarian syndrome explained in following:

1. Insulin Resistance: A defect in insulin action and secretion that leads to hyperinsulinemia and insulin resistance. The first recognition of an association between glucose intolerance and hyperandrogenism was made by Achard & Thiers (1921) and was called **'the diabetes of bearded women'.**[3]

The possible mechanism are:



2. Androgen production:

In view of the fact that androgen excess is the main feature of PCOS. Androgens are part of the steroid hormone family.[4] Abnormal regulation of the androgen forming enzyme (P450 C17) is thought to be the main causes for excess production of androgens from the ovaries and adrenal. the principal sources of androgen are: (a). Ovaries (b). Adrenal (c). Alternation of systemic metabolic.[5]

In the ovary, the first steps of androgen formation are perform in LH-stimulated cells, as these cells express the cytochrome P450c17 gene with the synthesis of DHEA (dehydroepiandrosterone) and androstenedione. Most of these precursors will be converted to estrogens by granulosa cells which express the enzyme P450 aromatase. Whereas, ovaries will also directly secrete androgens in the circulation, mainly as androstenedione and testosterone. Interestingly, ovarian androgens will not significantly feedback on LH production, such as an excess in free testosterone or androstenedione will not reduce ovarian production of these androgens in women, as opposed to men.[6] Therefore ovaries produce androgen excess due to :

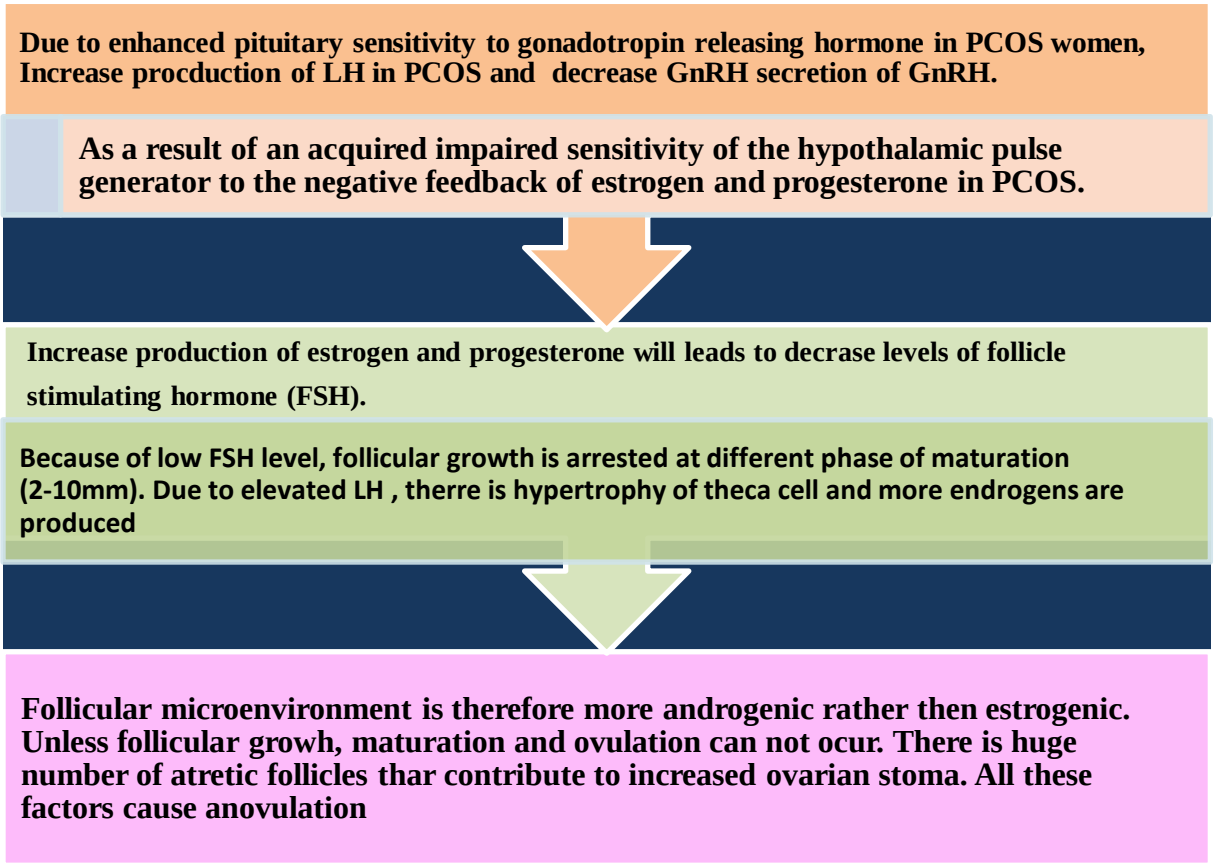
- Stimulation of theca cell by high LH
- P450C17 enzyme hyperfunction

- Defective aromatization of androgen to estrogen
- Stimulation of theca cell by IGF-1 or insulin growth factor-1.[7]

Adrenal glands are also encouraged to produce excess androgens by stress, P450 C17 enzyme hyperfunction and association with high prolactin levels.[7] In PCOS, the ovaries produce up to 60% of androgens, while the adrenals contribute the remaining 40%.[8] It is recognized that androgens produce from both the ovary and the adrenal which is fundamental sources of hyperandrogenemia in PCOS women.[9]

While ovarian androgen synthesis is suppressed by GnRH agonists, PCOS women were found to have higher androgen levels in comparison to normal women, thus suggesting adrenal overproduction of androgens. Similarly, when adrenal androgen synthesis is suppressed with dexamethasone, PCOS women again display higher androgen levels in comparison to normal women, indicating exaggerated ovarian production.[10]

3. Anovulation:



Prevention of Polycystic Ovarian Syndrome:

At the present time Obesity is the main cause of PCOS, reduce weight is very necessary to maintain ovaries function and normal monthly cycle. Therefore it will help to improve fertility rate. Therefore weight management is suggested as a first line management in overweight women with PCOS.[11] Awareness regarding healthy lifestyle, dietary habits and regular exercise or yoga are required for prevention and enhanced management of the disease.

Prevention would be important for PCOS but as specific etiological factors are not known. In order to use long-term intervention programs in children and adolescents, particularly rigid criteria must be used regarding proven safety and efficacy. In obese subjects, weight loss is very important, having beneficial effects on most aspects of the syndrome, such as subjective symptoms, infertility, hyperinsulinemia and related metabolic aberrations, and long-term health risks.[12]

There have been no clinical trials of primary prevention measures in PCOS. Lifestyle intervention like healthy dietary pattern, regular exercise and metformin therapy may prevent PCOS.[13]

The Androgen Excess PCOS Society (AEPCOS) statement on lifestyle modification in women with PCOS proposes lifestyle modification as the primary therapy in overweight and obese women with PCOS. A number of short-to medium-term studies demonstrate that modest weight loss (5–10% of initial body weight) improves metabolic, reproductive and psychological features of PCOS, including hyperandrogenism, insulin

resistance, dyslipidemia, glucose tolerance, menstrual function, ovulation, pregnancy, conception and quality of life.[14]

Dietary Modification : Eating the healthy foods and avoiding certain ingredients may helps in manage the PCOS symptoms. A nutrient diet can help to regulate hormones and menstrual cycle. It includes high-fiber vegetables, lean protein and anti-inflammatory foods such as turmeric and tomatoes, tomatoes, cabbage, spinach, almonds and walnuts, olive oil, fruits such as blueberries and strawberries, fatty fish high in omega-3 fatty acids. [16]

High-fiber foods can help combat insulin resistance by slowing down digestion and reducing the impact of sugar on the blood. There are some sources of high fiber diet like cruciferous vegetables such as broccoli, cauliflower, sprouts, red peppers, beans, lentils, almonds, berries, sweet potatoes, and pumpkin. [16]

Healthy eating habits relieve the symptoms of PCOS. Weight reduction may help to lower blood glucose levels, improve the utilization of body insulin and also helps to maintain normal hormonal levels. Even a 10% loss in body weight can help to regular menstrual cycle and help to get pregnant.[15]

Weight management through lifestyle modification combining dietary and exercise can be effective in improving reproductive function, as well as metabolic and psychological parameters. Reduced-energy diets (500-1000 kcal/day reduction) are effective options for weight loss and can reduce body weight by 7–10% over a period of 6–12 months.[16]

Dietary pattern should be nutritionally complete and appropriate for each life stage. A variety of approaches such as high carbohydrate diets, high dietary protein diets may be successful for achieving a reduced weight.[18]

Pernille R, Glintborg D, (2013) conducted a review of the existing literature on weight loss through lifestyle modification and metformin treatment in overweight women with PCOS. The result suggested that Weight loss is most effectively achieved through a 12-1500 kcal/day diet, which results in a clinically relevant weight loss. Metformin combined with a low calorie diet has subtle additive effect on weight loss and level of androgens when compared to diet alone. This study Concluded that weight loss through life style changes, preferably a low calorie diet, should be the first line treatment in overweight/obese women with PCOS. Metformin can be considered as an additional treatment but has subtle additive effect.[17]

Improve Emotional Health and Sleep: Sleep deprivation and chronic stress are major root causes for insulin resistance and micronutrient deficiencies. If women feel that there is a lack of sleep and stress then they should take adequate rest and sleep.[18]

Physical activity and Yoga: Yogic life style is a form of holistic mind-body medicine to reduce stress. Recent randomized controlled trial found holistic yoga program for 12 weeks to be significantly better than physical exercise in reducing Anti-Mullerian Hormone, Luteinizing Hormone and Testosterone, hirsutism and improved menstrual in PCOS women. Hence, yoga may be recommended as both a primary intervention and as adjunct with medical intervention for management of PCOS.[19]

Government guidelines recommend that at least 150 minutes a week of moderate aerobic activity or 75 minutes a week of vigorous aerobic activity in addition to two days of resistance training each week for weight management. These guidelines were affirmed in evidence-based guidelines for the management of PCOS.[20]

Anxiety is frequent observe factors among women with PCOS and yoga may provide an effective treatment for women with POCS to manage this problem. A study published in the International Journal of Yoga revealed that 12 weeks of a holistic yoga program in adolescent girls with PCOS was significantly effective than a physical exercise program in reducing anxiety related symptoms.[21]

It appear that yoga have also a positive impact on insulin and cholesterol levels in women with PCOS. It was significantly more effective than conventional physical exercises in improving glucose, lipid, and insulin resistance among the adolescent girls with PCOS. [22]

A systemic review suggested that reduced calorie diets and exercise interventions helps in weight loss and ovulation improvement.[23]

Yogic practices are found to be useful in PCOS which includes Surya Namaskara, Bhujangasana, Salabhasana, Dhanurasana, Trikonasana, Viparita Karni, Shoulder Stand , Halasana, Paschimottanasana, Baddha- konasana, Vibhagiya- Pranayama, Kapala Bhati, Suryanuloma Viloma, Savasana and OM Meditation.[24]

Verma A, Kumar S, Dei L and Dhiman K, 2015, conducted a study on management of PCOS by yoga practice .The result revealed that Surya Namaskar, Paschimottan Asan, Bhujangasana, Shalabhasan etc helps in weight reduction . This study concluded that daily yoga for 30 minutes with 4 Asanas, 4 Pranayama, meditation and shavasana helps in weight reduction and stress management which ultimately stabilize the normal function of hypothalmo- pituitary – ovarian axis and helps in cure of PCOS.[25]

Management of Polycystic Ovarian Syndrome:

Management of PCOS needs individualization concern of the patient and A multidisciplinary approach are require to treat PCOS. It is depends on her presenting sign and symptoms such menstrual disorder, infertility, obesity, hirsutism or combined of these symptoms. Basically, Five approaches are use to manage the PCOS which includes Clomiphene, Dexamethasone, Combination of Dexamethasone and clomiphene, Gonadotrophin therapy and GnRH agonist therapy.

There is no specific treatment of PCOS and it is directed only to treat the symptoms of individual patient. There is a indisputable need to understand and diagnose this syndrome early therefore, that holistic treatment of this syndrome can be initiated at the earliest, thereby preventing the long-term morbidity.[26]

Treatment is primarily targeted to correct the biochemical abnormalities which includes hyperandrogenemia, hyperinsulinemia, high serum estrogens, androgenic ovarian follicular microenvironment, hyper-secretion of LH, hyperprotectinemia, insulin resistance, low serum progesterone and low FSH.[27]

Weight reduction in obese or overweight women is the first line of treatment. it will helps to improves menstrual problems, fertility, insulin resistance, improve the metabolic syndrome and reproductive function.[28]

Management of PCOS If, Fertility not needed:

Management of Hyperandrogenemia: In this condition combine oral contraceptive pills are effective. it is generally given for adolescents with PCOS, different combinations of COCPs are available with heterogeneous estrogen and progestin preparations with varying pharmacological and clinical properties. Thus, Oral contraceptive pills (OCPs) contain estrogen which suppresses the LH, increases SHBG and decreases ovarian androgen production. These actions reduce the testosterone which reduce the acne and hirsutism problems in PCOS.[29] Moreover, combined oral contraceptive choice of treatment to prevent endometrial hyperplasia and abnormal bleeding.[30]

The progestins used in OCP are considered as per degree of androgenic properties as they are testosterone derivatives. Newer progestins like norethindrone, desogestrel, and norgestimate comprise androgenic action.[31]

A randomized controlled trial conducted on desogestrel/ethinyl estradiol in addition spironolactone versus cyproterone acetate/ethinyl estradiol in the treatment of polycystic ovary syndrome. The result revealed that both group have significantly decreased acne, free androgen index and increased sex hormone-binding globulin levels. The regular withdrawal bleeding was obtained in both groups. this study concluded that both regimens had efficacy on hyperandrogenism after three cycles of therapy and without any changes in metabolic parameters.[32]

International evidence-based guideline for the assessment and management of polycystic ovary syndrome (2018), COCPs alone recommended are effective in adult women and adolescents with PCOS for management of hyperandrogenism and irregular menstrual cycles.[33]

Management of Hirsutism:

Hirsutism is a troublesome hyper-androgenic manifestation of PCOS which may require at least 6 months of treatment. As per Cochrane review, (2015) suggested that the most effective first-line therapy for mild hirsutism is oral contraceptives. Meanwhile, Spironolactone 100 mg OD daily and flutamide 250 mg BD daily are safe but the evidence for their effectiveness is minimal.[34]

Anti-androgens such as spironolactone can substantially reduce hair diameter over 12 months of use.[35] The initial dose of spironolactone 50–100 mg is best used in combination with OCPs to improved the outcome.[36] Moreover, cosmetic therapy along with OCPs is recommended in cases of women with hirsutism, but the response to treatment is usually expected after 6–9 months of this therapy due to long hair growth cycle. If needed, antiandrogen to be added after 6 months of OCPs therapy.[37]

Hormonal medications (OCPs) play a important role in the management of hirsutism. Whereas, hair removal methods are frequently required adjunct to minimize the appearance of hirsutism. Temporary methods for hair removal include bleaching, shaving, chemical depilatories, tweezing and waxing. The potential side effects of temporary methods may include skin irritation, allergic, scarring, and folliculitis. There are also topical creams, such as eflornithine 13.9%, which acts at the level of the hair follicle and is most effective if used in conjunction with temporary hair removal methods.[38]

Eflornithine is an approved drug by the Food and Drug Administration for the treatment of unwanted facial hair growth. It is an irreversible inhibitor of l-ornithine decarboxylase which an enzyme that control hair growth.[39]

Permanent hair removal methods include electrolysis, thermolysis and laser treatment. Laser treatment is effective for treating large areas with fewer side effects than electrolysis or thermolysis. Overall, laser treatment is most effective in patients with light skin and dark hair.[40]

Oral contraceptives have been found effective for acne in PCOD and especially in cases of deep-seated nodules and relapsing acne on isotretinoin. Huber et al. have found 30–60% reduction in inflammatory acne count within 3–6 months of OCPs treatment.[41]

Management of Metabolic Syndrome:

Metabolic syndrome is defined as a combination of abnormal glucose metabolism, elevated blood pressure, abnormal lipid profile and obesity.[42]

The prevalence of metabolic syndrome is high as 33% in women with PCOS and also associated with long-term consequences such as cardiovascular disease (CVD), type II diabetes, cancers, sleep disturbance and psychological problems. Exercise and dietary regulation are important components of a healthy lifestyle which have demonstrated significant improvements in symptoms of PCOS.[43]

Management of metabolic syndrome should focus on risk factors and individual components. At present, lifestyle modification is the only recommended intervention for the management of metabolic problems in PCOS. Insulin resistance appears to be important in the pathogenesis of PCOS and subsequent metabolic syndrome.

Improvement in lifestyle modification including diet, exercise and stress reduction techniques is the future in treatment of metabolic syndrome in PCOS. [44] Reduced body weight is associated with a decrease in metabolically active visceral fat, which leads to decreased insulin resistance and an optimized lipid profile.[45]

Research finding regarding stress reduction revealed that low-frequency electro acupuncture (EA) may be useful in the treatment of hyperandrogenism and menstrual frequency. In a randomized controlled trial of 84 women with PCOS for 16-week regimen of EA compared to 16 weeks physical exercise. Interestingly, the magnitudes of changes in testosterone and menstrual frequency were significantly greater in 16-week regimen of EA women.[46]

The Medical Management of metabolic syndrome in PCOS need multiple strategies which includes management of insulin resistance, use of anti-obese agents and improved lipid profiles. Hyperinsulinemia increases the risk of dyslipidemia, cardiovascular disease and diabetes mellitus. Therefore, used of insulin sensitizing agent helped to overcome this problem .[47]

Women with PCOS with BMI>25 are often found insulin resistance. Obese women with PCOS often suffer from impaired glucose tolerance or type to diabetes. Hence, correction of their metabolic abnormality along with weight reduction give satisfactory result. Treatment by metformin is found to reduce hyperinsulinemia and hyperandrogenemia.[48]

Treatment of menstrual insufficiency for infertile women have two choices which includes Medeoxyprogesterone and Combination oral contraceptive pill (OCP). Medeoxyprogesterone regimen include 10 mg 1 tab daily for first 10 days of each calendar month helps to reduce endometrial hyperplasia and alteration on secretory change in it followed by its cyclical shedding. [49]

According British National formulary (2012), Metformin is a oral antidiabetic therapy used for management of PCOS. It works in the management of PCOS as lowers serum insulin level, lowers free testosterone, lowers LH, increase SHBG and normalize FSH:LH ratio. This therapy should be started at the follicular phase of the menstrual cycle with a dose of 500mg/day for 7 days. Thus, it is to be increased at weekly interval by 500mg/day upto maximum 1500mg/day generally for six months initially under follow-up. Rosiglitazone is insulin sensitizer is indicated in clomiphene resistant which given 4mg BD daily from 5 to 9 day of the menstrual cycle along with clomiphene for the management of PCOS.[50]

A systematic review of 6 RCT, that assessed hyperandrogenic symptoms and other non-fertility symptoms, compared metformin versus the combined oral contraceptive pill. The finding suggested that Metformin was less effective than OCP in reducing serum androgen levels in the management of PCOS.[51]

Another medication, Inositols are compounds which have insulin-mimetic properties, particularly in the isomers myoinositol (MI) and d-chiroinositol. They works as the activation of insulin receptors, reduces serum insulin, serum androgen level and considered a mediators of insulin action.[52]. Thereby it reduces hirsutism and acne, triglyceride level and other metabolic abnormalities in PCOS. Various studies have demonstrated that administration of d-chiroinositol leads to decreased basal insulin levels, an improved lipid profile and reduced systolic blood pressure in the management of PCOS.[53]

Obesity is one of the frequently occurring feature of PCOS and it has been found that simple weight reduction is associated with the following favorable changes such as normalization of the hormonal disturbances, improve hirsutism, resumption of regular ovulation and improved pregnancy rate. Whereas, weight reduction also decrease insulin resistance, testosterone and increased SHBG.[54]

Pharmacotherapy for the management of obesity in PCOS used Anti-obesity agents in which includes Orlistat, rimonabant and sibutramine. Orlistat is an irreversible gastric lipase inhibitor that prevents the breakdown of dietary fat. Sibutramine and rimonabant have been withdrawn over safety concerns. Orlistat works as induces significant and sustainable weight loss with similar efficacy to metformin in PCOS. Hence, it is also associated with an improved lipid profile, including significant reductions in the levels of total cholesterol, low-density lipoprotein and triglycerides.[55]

A randomized study conducted on to assess the effect of Orlistat on obese women with metabolic syndrome. the result suggested that 43.5% of women with associated improvements in anthropometry, insulin resistance, lipid profile and blood pressure. it also showed favorable effect in cardiovascular risk. However, this study concluded that further research are required to assess the use of Orlistat in women with PCOS and metabolic syndrome.[56]

Management of PCOS if, fertility Desire:

Infertility is a stressful medical and psychosocial problem afflicting all expecting couples to get pregnant. There have to use certain measure to manage infertility or subfertilty related to PCOS. Major cause of menstrual irregularity and anovulation is polycystic ovary syndrome which leads to infertility. Out of all couples seeking treatment for infertility, 30% of cases are due to anovulation. It is estimated that 90% of anovulation cases are actually caused by PCOS.[57]

The Management of infertility due to PCOS is induction of ovulation beside management of metabolic syndrome. Various methods have been deployed to treat the anovulation as a treatment options for infertility in women with PCOS.[58]

Lifestyle Change is considered the first-line treatment for infertility in obese women with PCOS. Preconception counseling, administering folic acid, encouragement of physical activity and identification of risk factors is helpful to manage infertility in PCOS.[60]

Obesity is related to anovulation and pregnancy loss. Hence, with ovulation induction methods such as clomiphene citrate, gonadotropins, Letrozole, and ovarian drilling show poor response of induction treatment. Weight reduction is the first line management to gain fertility with pharmacological agents. There are various benefits of weight reduction in PCOS management.[59]

Several research findings suggested that reduce weight improved the ovarian functions. Similar to the American societies indicate that weight loss as 5–10% of body weight can regularize menses and improve response to ovulation induction and fertility medications.[60]

The second line treatment of infertility related to PCOS is **Pharmacological agent**. Several pharmacologic agents have been used to induce ovulation. These drugs include clomiphene citrate, metformin, Letrozole, gonadotropins, inositol, and Tamoxifen.[61]

Ovulation Induction: **Clomiphene citrate** is a first-line drug in treating anovulation with correction of metabolic syndrome in women with PCOS. Letrozole, metformin and follicle-stimulating hormone are some of the other ways to treat this condition. In unresponsive cases, FSH or human menopausal Gonadotropin (HMG) along with human chorionic Gonadotrophin (hCG) may be administered.[62]

Clomiphene citrate has both estrogenic agonist and antagonist effects. It act by blocking the estrogen receptors in the hypothalamus to increase the endogenous follicle-stimulating hormone (FSH) for improve ovulation. Clomiphene citrate have been found to be inferior drugs such as Letrozole compared to other pharmacologic agents used for induction of ovulation.[63]

Initial dose recommend of Clomiphene citrate is 50mg, maximum 250mg between 2 to 5 days of menstruation for 5 days, ovulation expecting 5-7 days after the last day of therapy. it is generally given for 6 menstrual cycle. [64] The ovulation rate may reach 75 to 80% with a conception rate of 22% per cycle and a cumulative pregnancy rate between 60 and 70% in six cycles.[48] Throughout Clomiphene citrate therapy couple have to instruct regarding sexual intercourse as per following daily or alternative days beginning 5-7 days after the last dose of Clomiphene citrate, several time for 24-48 hours after colour change in urine when tested by LH kit and number of the times over 24-46hrs following inj. hCG. [DC] Whereas, Clomiphene citrate in combination with metformin increase 1.8 times chance of pregnancy compared to the clomiphene citrate alone.[65]

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